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=> d stat que
L1             1 SEA FILE=REGISTRY TSP2/CN
L2             1 SEA FILE=REGISTRY "THROMBOSPONDIN 2 (CATTLE CLONE P268C1
                 PRECURSOR)"/CN
L3           135 SEA FILE=HCAPLUS L1 OR L2 OR TSP2 OR THROMBOSPONDIN2 OR (TSP
                 OR THROMBOSPONDIN)(W)2
L4            16 SEA FILE=HCAPLUS L3 AND CELL(W)PROLIFER?


=> d ibib abs hitrn l4 1-16

L4   ANSWER 1 OF 16  HCAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:         2002:501936  HCAPLUS
TITLE:                    Thrombospondin 2 inhibits
                          microvascular endothelial cell
                          proliferation by a caspase-independent
                          mechanism
AUTHOR(S):                Armstrong, Lucas C.; Bjorkblom, Benny; Hankenson, Kurt
                          D.; Siadak, Anthony W.; Stiles, Charlotte E.;
                          Bornstein, Paul
CORPORATE SOURCE:         Department of Biochemistry, University of Washington,
                          Seattle, WA, 98195, USA
SOURCE:                   Molecular Biology of the Cell (2002), 13(6), 1893-1905
                          CODEN: MBCEEV; ISSN: 1059-1524
PUBLISHER:                American Society for Cell Biology
DOCUMENT TYPE:            Journal
```

LANGUAGE: English
AB The matricellular protein **thrombospondin 2** (**TSP2**) regulates a variety of cell-matrix interactions. A prominent feature of **TSP2**-null mice is increased microvascular d., particularly in connective tissues synthesized after injury. We investigated the cellular basis for the regulation of angiogenesis by **TSP2** in cultures of murine and human fibroblasts and endothelial cells. Fibroblasts isolated from murine and human dermis synthesize **TSP2** mRNA and secrete significant amts. of immunoreactive **TSP2**, whereas endothelial cells from mouse lung and human dermis did not synthesize **TSP2** mRNA or protein. Recombinant mouse **TSP2** inhibited growth of human microvascular endothelial cells (HMVECs) mediated by basic fibroblast growth factor, insulin-like growth factor-1, epidermal growth factor, and vascular endothelial growth factor (VEGF). HMVECs exposed to **TSP2** in the presence of these growth factors had a decreased proportion of cells in S and G2/M phases. HMVECs cultured with a combination of basic fibroblast growth factor, insulin-like growth factor-1, and epidermal growth factor displayed an increased proportion of nonviable cells in the presence of **TSP2**, but the addn. of VEGF blocked this **TSP2**-mediated impairment of cell viability. **TSP2**-mediated inhibition of DNA synthesis by HMVECs in the presence of VEGF was not affected by the broad-spectrum caspase inhibitor zVAD-fmk. Similar findings were obtained with TSP1. Taken together, these observations indicate that either **TSP2** or TSP1 can inhibit HMVEC proliferation by inhibition of cell cycle progression and induction of cell death, but the mechanisms responsible for **TSP2**-mediated inhibition of cell cycle progression are independent from those leading to cell death.
REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:333668 HCAPLUS
DOCUMENT NUMBER: 137:4978
TITLE: Interactions of thrombospondins with .alpha.4.beta.1 integrin and CD47 differentially modulate T cell behavior
AUTHOR(S): Li, Zhuqing; Calzada, Maria J.; Sipes, John M.; Cashel, Jo Anne; Krutzsch, Henry C.; Annis, Douglas S.; Mosher, Deane F.; Roberts, David D.
CORPORATE SOURCE: Laboratory of Pathology, National Cancer Institute, National Institutes of Health, Bethesda, MD, 20892, USA
SOURCE: Journal of Cell Biology (2002), 157(3), 509-519
CODEN: JCLBA3; ISSN: 0021-9525
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Thrombospondin (TSP)-1 has been reported to modulate T cell behavior both pos. and neg. The authors found that these opposing responses arise from interactions of TSP1 with two different T cell receptors. The integrin .alpha.4.beta.1 recognizes an LDVP sequence in the N-terminal domain of TSP1 and was required for stimulation of T cell adhesion, chemotaxis, and matrix metalloproteinase gene expression by TSP1. Recognition of TSP1 by

T cells depended on the activation state of .alpha.4.beta.1 integrin, and TSP1 inhibited interaction of activated .alpha.4.beta.1 integrin on T cells with its counter receptor vascular cell adhesion mol.-1. The .alpha.4.beta.1 integrin recognition site is conserved in **TSP2**. A recombinant piece of **TSP2** contg. this sequence replicated the .alpha.4.beta.1 integrin-dependent activities of TSP1. The .beta.1 integrin recognition sites in TSP1, however, were neither necessary nor sufficient for inhibition of T **cell proliferation** and T cell antigen receptor signaling by TSP1. A second TSP1 receptor, CD47, was not required for some stimulatory responses to TSP1 but played a significant role in its T cell antigen receptor antagonist and antiproliferative activities. Modulating the relative expression or function of these two TSP receptors could therefore alter the direction or magnitude of T cell responses to TSPs.

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:206253 HCAPLUS
DOCUMENT NUMBER: 136:399094
TITLE: The secreted protein **thrombospondin 2** is an autocrine inhibitor of marrow stromal **cell proliferation**
AUTHOR(S): Hankenson, Kurt D.; Bornstein, Paul
CORPORATE SOURCE: Department of Biochemistry, University of Washington, Seattle, WA, USA
SOURCE: Journal of Bone and Mineral Research (2002), 17(3), 415-425
CODEN: JBMREJ; ISSN: 0884-0431
PUBLISHER: American Society for Bone and Mineral Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Marrow stromal cells (MSCs) are obtained in increased no. from mice in which the **thrombospondin 2** (**TSP2**) gene is disrupted, and these cells show increased DNA synthesis in vitro. To examine more closely the role of **TSP2** in the physiol. and osteogenic differentiation of MSCs, an in-depth characterization of **TSP2**-null MSCs was conducted. Detn. of **TSP2** protein content by Western anal. and RNA levels by reverse-transcription polymerase chain reaction (RT-PCR) indicated that MSCs are the primary source of **TSP2** in the marrow and secrete abundant **TSP2** into culture medium. Morphol., the **TSP2**-null and wild-type (WT) cell populations were similar and by flow cytometry contained equiv. nos. of CD44+, Mac1+, intercellular adhesion mol.-1 (ICAM-1+), and ScaI+ cells. **TSP2**-null cells showed delayed mineralization assocd. with an increased rate of proliferation. Consistent with this finding, there was a decrease in expression of collagen and osteocalcin RNA by **TSP2** -null MSCs on day 7 and increased osteopontin expression on day 7 and day 14. In add-back expts., recombinant **TSP2** produced a dose-dependent decrease in proliferation. This redn. was assocd. with an accumulation of **TSP2**-treated cells in the G1 phase of the cell cycle and did not result from an increase in apoptosis. When **TSP2** treatment was terminated, the cell population reentered the S phase. We conclude that the increased endosteal bone formation obsd. in **TSP2**

-null mice results primarily from the failure of **TSP2** to regulate locally MSC cell cycle progression.
REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:143280 HCAPLUS
DOCUMENT NUMBER: 136:189386
TITLE: Delivery of thrombospondin from implantable tissue matrices
INVENTOR(S): Detmar, Michael; Vacanti, Joseph P.; Streit, Michael; Stephen, Antonia E.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 16 pp., Cont.-in-part of U.S. Ser. No. 536,087.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002022592	A1	20020221	US 2001-822161	20010330
US 2002031500	A1	20020314	US 2001-770339	20010126

PRIORITY APPLN. INFO.:
US 1999-127221P P 19990331
US 2000-178842P P 20000127
US 2000-536087 A2 20000324
US 2001-770339 A2 20010126

AB Normal cells, such as fibroblasts or other tissue or organ cell types, are genetically engineered to express biol. active, anti-angiogenic compds., in particular, **thrombospondin-2**. These cells are seeded into a matrix for implantation into the patient to be treated. Cells may also be engineered to include a lethal gene, so that implanted cells can be destroyed once treatment is completed. Cells can be implanted in a variety of different polymer matrixes. In a preferred embodiment, these matrixes are implantable and biodegradable over a period of time equal to or less than the expected period of treatment, during which the engrafted cells form a functional tissue producing the desired biol. active agent for longer periods of time. These devices and strategies are used as delivery systems, which may be implanted by std. or minimally invasive implantation techniques, for delivery of anti-angiogenic mols., esp. **thrombospondin-2**, for the treatment of a variety of conditions that produce abnormal growth, including treatment of malignant and benign neoplasias, vascular malformations (hemangiomas), inflammatory conditions, keloid formation and adhesion, endometriosis, congenital or endocrine abnormalities, and other conditions that can produce abnormal growth such as infection. Bioimplants maintained **TSP-2** secretion over prolonged time periods, resulting in a potent inhibition of tumor growth and angiogenesis of three different, highly aggressive malignant tumors implanted at a distant site.

L4 ANSWER 5 OF 16 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2002:131029 HCAPLUS
DOCUMENT NUMBER: 136:364145
TITLE: Human **thrombospondin 2** inhibits proliferation of microvascular endothelial cells
AUTHOR(S): Tomh, Yasushi; Kamochi, Junichiro; Yamazaki, Hitoshi; Sawa, Nobuko; Tokunaga, Tetsuji; Ohnishi, Yasuyuki; Kijima, Hiroshi; Ueyama, Yoshito; Tamaoki, Norikazu; Nakamura, Masato
CORPORATE SOURCE: Departments of Pathology, Tokai University School of Medicine, Bohseidai, Isehara, Kanagawa, Japan
SOURCE: International Journal of Oncology (2002), 20(2), 339-342
CODEN: IJONES; ISSN: 1019-6439
PUBLISHER: International Journal of Oncology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This study was performed to characterize human **thrombospondin 2** (**TSP2**). **TSP2** has recently attracted attention as an endogenous neg. regulator of angiogenesis in tumorigenesis. We cloned and transfected human **TSP2** cDNA into the human colon cancer cell line SW-480. Stable transfectants (**TSP2**-1, **TSP2**-6) overexpressing **TSP2** were established. Growth characteristics of **TSP2**-transfectants were investigated in vitro and in vivo. **TSP2**-transfectants showed similar growth properties to vector-transfectants and wild-type SW-480 cells. The overexpression of transfected human **TSP2** cDNA did not affect proliferation of SW-480 cells. When the conditioned media of **TSP2**-transfectants were added to cultures of bovine pulmonary microvascular endothelial cells (BPMEC), the BPMEC proliferation was significantly inhibited. These results suggested that human **TSP2** is a potential inhibitor of angiogenesis.
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:204569 HCAPLUS
DOCUMENT NUMBER: 135:268042
TITLE: Transcription factor ATF3 partially transforms chick embryo fibroblasts by promoting growth factor-independent proliferation
AUTHOR(S): Perez, Sandrine; Vial, Emmanuel; Van Dam, Hans; Castellazzi, Marc
CORPORATE SOURCE: Unite de Virologie Humaine, Institut National de la Sante et de la Recherche Medicale (INSERM-U412), Ecole Normale Superieure, Lyon, 69364, Fr.
SOURCE: Oncogene (2001), 20(9), 1135-1141
CODEN: ONCNES; ISSN: 0950-9232
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Activating Transcription Factor 3 (ATF3) is a member of the bZip family of transcription factors. Previous studies in mammalian cells suggested that like other bZip family members e.g. Jun and Fos, ATF3 might play a role in the control of **cell proliferation** and participate in

oncogenic transformation. To investigate this putative ATF3 function directly, the rat ATF3 protein was compared with v-Jun for its ability to transform primary cultures of chick embryo fibroblasts (CEFs). Like CEFs accumulating v-Jun, CEFs accumulating the ATF3 protein displayed a typical, fusiform morphol., assocd. with an enhanced capacity to grow in medium with reduced amt. of serum. However, in contrast to v-Jun-transformed CEFs, the ATF3 overexpressing cells could not promote colony formation from single cells in agar. Partial transformation induced by ATF3 was found to be assocd. with repression of multiple cellular genes that are also down-regulated by v-Jun, including those coding for the extracellular components fibronectin, decorin, **thrombospondin 2**, and the pro-apoptotic protein Par-4. These data demonstrate that, at least in primary avian cells, rat ATF3 possesses in intrinsic oncogenic potential. Moreover, the results suggest that ATF3 might induce growth factor independence by down-regulating a subset of the genes repressed by v-Jun.

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:90683 HCAPLUS
DOCUMENT NUMBER: 135:32059
TITLE: Thrombospondin-1 and -2 in node-negative breast cancer: Correlation with angiogenic factors, p53, cathepsin D, hormone receptors and prognosis
AUTHOR(S): Gasparini, Giampietro; Toi, Masakazu; Biganzoli, Elia; Dittadi, Ruggero; Fanelli, Massimo; Morabito, Alessandro; Boracchi, Patrizia; Gion, Massimo
CORPORATE SOURCE: Division of Medical Oncology, Azienda Complesso Ospedaliero "San Filippo Neri", Rome, I-00135, Italy
SOURCE: Oncology (2001), Volume Date 2000, 60(1), 72-80
CODEN: ONCOBS; ISSN: 0030-2414
PUBLISHER: S. Karger AG
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Thrombospondins (TSPs) are a multigene family of five secreted glycoproteins involved in the regulation of **cell proliferation**, adhesion and migration. Two members of the TSP family, namely TSP-1 and **TSP-2**, are also naturally occurring inhibitors of angiogenesis. The aim of the present study was to det. the prognostic significance of the detn. of TSP-1 and -2 and their correlation with the angiogenic peptides vascular endothelial growth factor (VEGF) and thymidine phosphorylase (TP), as well as with other biol. and clinicopathol. features investigated. We evaluated a series of 168 women with node-neg. breast cancer with a median follow-up period of 66 mo, not treated with adjuvant therapy. The cytosolic levels of TSP-1 and -2 were detd. in the primary tumor by a com. available immunometric assay. We found that 166 tested tumors had measurable levels of TSP-1 and -2 protein (median value 5.978, range 0.579-31.410 ng/mg of protein). On the basis of Spearman's rank correlation coeff., a weak inverse assocn. of TSP-1 and -2 with tumor size and cathepsin D was found. Moreover, principal component anal. on ranks evidenced a poor assocn. between TSP-1 and -2, VEGF and TP. The results of the clin. outcome were analyzed by both univariate and multivariate [for relapse-free survival (RFS) only]

Cox regression models. TSP-1 and -2 were not significant prognostic factors in univariate anal. for either RFS (p = 0.427) or overall survival (p = 0.069). To investigate the "angiogenic balance hypothesis", bivariate analyses were performed to investigate the interactions of TSP-1 and -2 with VEGF, TP or p53, but none were included in the selected models. Finally, in multivariate anal. for RFS a baseline model, previously defined in a larger case series and inclusive of VEGF, TP and their interaction was adopted. It was highly significant (p = 0.002, Harrell c statistic value of 0.703); but when TSP-1 and -2 were added, their contribution was negligible (p = 0.731, Harrell c statistic value of 0.705). The results of this.

REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:707001 HCAPLUS
DOCUMENT NUMBER: 133:276326
TITLE: **Thrombospondin-2** for control of angiogenesis and unwanted **cell proliferation**
INVENTOR(S): Detmar, Michael; Streit, Michael
PATENT ASSIGNEE(S): The General Hospital Corp., USA
SOURCE: PCT Int. Appl., 73 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000057899	A1	20001005	WO 2000-US7835	20000324
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1171151	A1	20020116	EP 2000-918344	20000324
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: US 1999-127221P P 19990331
WO 2000-US7835 W 20000324

AB The invention features a method of treating a disorder characterized by unwanted angiogenesis and/or unwanted cellular proliferation, e.g., unwanted skin or prostate **cell proliferation**, by increasing a **TSP-2** activity. The invention also features methods of identifying compds. which modulate, e.g., inhibit or promote, **TSP-2** activity, and methods of evaluating if a subject is at risk for a disorder characterized by unwanted angiogenesis and/or unwanted cellular proliferation. The invention also features

fragments and analogs of **TSP-2** which can be used to treat such disorders.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:324812 HCAPLUS
DOCUMENT NUMBER: 133:220799
TITLE: Increased marrow-derived osteoprogenitor cells and endosteal bone formation in mice lacking **thrombospondin 2**
AUTHOR(S): Hankenson, Kurt D.; Bain, Steven D.; Kyriakides, Themis R.; Smith, Erica A.; Goldstein, Steven A.; Bornstein, Paul
CORPORATE SOURCE: Department of Biochemistry, University of Washington, Seattle, WA, USA
SOURCE: Journal of Bone and Mineral Research (2000), 15(5), 851-862
CODEN: JBMREJ; ISSN: 0884-0431
PUBLISHER: American Society for Bone and Mineral Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The phenotype of **thrombospondin 2** (**TSP2**)-null mice includes abnormalities in collagen fibrils and increases in ligamentous laxity, vascular d., and bleeding time. In this study, analyses by computerized tomog. (CT) revealed that cortical d. was increased in long bones of **TSP2**-null mice. Histomorphometric anal. showed that the mid-diaphyseal endosteal bone formation rate (BFR) of **TSP2**-null mice was increased in comparison with that of wild-type (WT) animals. Although microgeometric anal. showed that periosteal and endosteal radii were reduced, the mech. properties of femurs from **TSP2**-null mice were not significantly different from those of controls, presumably because of the concomitant increase in endosteal bone mass. Bone loss in ovariectomized mice was equiv. for WT and mutant mice, a finding that indicates that **TSP2**-null animals are capable of normal bone resorption. To further explore the cellular basis for the increased endosteal BFR in **TSP2**-null mice, marrow stromal cells (MSCs) were isolated and examd. in vitro. These cells were found to be present in increased nos. in a colony forming unit (CFU) assay and showed an increased rate of proliferation in vitro. We conclude that **TSP2** regulates the proliferation of osteoblast progenitors, directly or indirectly, and that in its absence endosteal bone formation is increased.

REFERENCE COUNT: 74 THERE ARE 74 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:14359 HCAPLUS
DOCUMENT NUMBER: 132:249290
TITLE: Expression of angiostatic factors in colorectal cancer
AUTHOR(S): Yoshida, Yukiko; Oshika, Yoshiro; Fukushima, Yoshitaka; Tokunaga, Tetsuji; Hatanaka, Hiroyuki; Kijima, Hiroshi; Yamazaki, Hitoshi; Ueyama, Yoshito; Tamaoki, Norikazu; Miura, Soichiro; Nakamura, Masato

CORPORATE SOURCE: Department of Pathology, Tokai University School of Medicine, Kanagawa, 259-1193, Japan
SOURCE: International Journal of Oncology (1999), 15(6), 1221-1225
CODEN: IJONES; ISSN: 1019-6439
PUBLISHER: International Journal of Oncology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Angiogenesis plays an important role in growth and proliferation of cancer. Various angiogenic and angiostatic factors regulate angiogenesis. The authors examd. expression of genes encoding various angiostatic factors: thrombospondin 1 (TSP1), **thrombospondin 2** (**TSP2**), brain-specific angiogenesis inhibitor 1 (BAI1) and angiopoietin 2 (AGP2) in 62 colorectal cancers and 40 samples of extraneoplastic colon mucosa. The expression of the angiostatic factors **TSP2** and AGP2 were significantly increased in the cancerous mucosa as compared to these in extraneoplastic mucosa, while the increase in TSP1 expression was not significant. BAI1 expression was slightly decreased in the cancer tissue. These results suggested that specific types of angiostatic factors might have protective roles against cancer **cell proliferation** via dormancy due to hyponutrition caused by decreased vascularity.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 11 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:368612 HCAPLUS
DOCUMENT NUMBER: 131:143072
TITLE: Mice that lack the angiogenesis inhibitor, **thrombospondin 2**, mount an altered foreign body reaction characterized by increased vascularity
AUTHOR(S): Kyriakides, Themis R.; Leach, Kathleen J.; Hoffman, Allan S.; Ratner, Buddy D.; Bornstein, Paul
CORPORATE SOURCE: Department of Biochemistry, University of Washington, Seattle, WA, 98195, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1999), 96(8), 4449-4454
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Disruption of the **thrombospondin 2** gene (Thbs2) in mice results in a complex phenotype characterized chiefly by abnormalities in fibroblasts, connective tissues, and blood vessels. Consideration of this phenotype suggested to the authors that the foreign body reaction (FBR) might be altered in **thrombospondin 2** (**TSP2**)-null mice. To investigate the participation of **TSP2** in the FBR, polydimethylsiloxane (PDMS) and oxidized PDMS (ox-PDMS) disks were implanted in **TSP2**-null and control mice. Growth of **TSP2**-null and control skin fibroblasts in vitro also was evaluated on both types of disks. Normal fibroblasts grew as a monolayer on both surfaces, but attachment of the cells to ox-PDMS was weak and sensitive to movement. **TSP2**-null fibroblasts grew as aggregates on both

surfaces, and their attachment was further compromised on ox-PDMS. After a 4-wk implantation period, both types of PDMS elicited a similar FBR with a collagenous capsule in both **TSP2**-null and control mice. However, strikingly, the collagenous capsule that formed in **TSP2** -null mice was highly vascularized and thicker than that formed in normal mice. In addn., abnormally shaped collagen fibers were obsd. in capsules from mutant mice. Thus, the presence or absence of an extracellular matrix component, **TSP2**, can influence the nature of the FBR, in particular its vascularity. The expression of **TSP2** therefore could represent a mol. target for local inhibitory measures when vascularization of the tissue surrounding an implanted device is desired.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:424639 HCAPLUS
DOCUMENT NUMBER: 129:63073
TITLE: Hormonally regulated components of the adrenocortical cell environment and the control of adrenal cortex homeostasis
AUTHOR(S): Feige, Jean-Jacques; Keramidas, M.; Chambaz, E. M.
CORPORATE SOURCE: Laboratoire Biochemie Regulations Cellulaires Endocrines, Departement Biologie Moleculaire Structurale, CEA Grenoble, Grenoble, F-38054, Fr.
SOURCE: Hormone and Metabolic Research (1998), 30(6/7), 421-425
CODEN: HMMRA2; ISSN: 0018-5043
PUBLISHER: Georg Thieme Verlag
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 42 refs. is given on the ongoing characterization of the structure and functions of the extracellular matrix components secreted by adrenocortical cells and their possible implication in the hormonal regulation of adrenal cortex homeostasis is discussed. The extracellular matrix (ECM) strongly contributes to the regulation of **cell proliferation** and cell differentiation, and thereby of embryonic development and adult tissue homeostasis. Fibronectin (FN) and laminin (LN) are both major adhesive proteins for adrenocortical cells. FN is synthesized by bovine fasciculata cells in primary culture, and its synthesis is stimulated by TGF.beta.1, TGF.beta.2, and FGF-2 but is not modified by IGF-1 or by the hormones ACTH and angiotensin II. LN is also synthesized by bovine fasciculata cells and its synthesis is specifically stimulated by ACTH. Both proteins are haptotactic and chemotactic for adrenocortical cells, suggesting a physiol. role in adrenocyte migration. Their distribution in the adrenal gland is quite distinct. LN is uniformly present in the steroidogenic cells from the 3 zones, whereas FN is abundant in the fibrovascular structures of the capsule and the cortex. ACTH treatment of adrenocortical cells strongly induces the expression and secretion of **thrombospondin-2** (**TSP2**), a large trimeric matricellular protein. The multimodular structure of **TSP2** is the support of a variety of biol. functions. **TSP2** promotes attachment but prevents spreading of adrenocortical cells. On the other hand, **TSP2** induces the activation of latent TGF.beta. through an indirect mechanism and is anti-angiogenic in vitro. The

overall distribution of **TSP2** in the glomerulosa and fasciculata zones of the adrenal cortex, and its absence from the reticularis zone, argue in favor of a role in the protection of adrenocortical cells against apoptosis. In the adrenal cortex, 5 main biol. functions are potentially regulated by components of the extracellular matrix: stem cell commitment into the adrenocyte differentiation pathway, terminal differentiation toward the 3 distinct adrenocyte phenotypes, centripetal migration, apoptosis, and the formation of the capillary network. Future studies will aim at deciphering which extracellular component(s) is involved in each of these regulations.

L4 ANSWER 13 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:147507 HCAPLUS
DOCUMENT NUMBER: 126:195735
TITLE: Endothelial cell mitogenesis induced by LPA: inhibition by thrombospondin-1 and **thrombospondin-2**
AUTHOR(S): Panetti, Tracee Scalise; Chen, Hui; Misenheimer, Tina M.; Getzler, Sarah B.; Mosher, Deane F.
CORPORATE SOURCE: Departments of Medicine and Biomolecular Chemistry, University of Wisconsin-Madison, MADISON, WI, 53706, USA
SOURCE: Journal of Laboratory and Clinical Medicine (1997), 129(2), 208-216
CODEN: JLCMAK; ISSN: 0022-2143
PUBLISHER: Mosby-Year Book
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We examd. the effects of thrombospondin-1 (TSP1) and **thrombospondin-2** (**TSP2**) on the uptake of tritiated thymidine by bovine aortic endothelial (BAE) cells in response to two growth factors, basic fibroblast growth factor (bFGF) and lysophosphatidic acid (LPA). The bFGF and LPA stimulate **cell proliferation** through distinct receptors that have convergent signaling pathways. The doses of LPA that trigger proliferation of BAE cells, which have not been reported previously, were 1 to 30 .mu.mol/L, as opposed to the 5 to 100 .mu.mol/L concns. required to stimulate proliferation of human foreskin fibroblasts. Baseline mitogenic activity and activity stimulated by either bFGF or LPA on BAE cells was inhibited by human TSP1 purified from platelets or a recombinant source with a similar dose response. These results demonstrate that the anti-proliferative effect of platelet TSP1 is not caused by contaminants from the stimulated platelet. Recombinant mouse **TSP2** inhibited BAE **cell proliferation** in response to LPA in a dose range similar to that of TSP1. Inasmuch as **TSP2** does not activate latent TGF.beta.1, these results show that inhibition of angiogenesis by TSPs is not related to control of activation of TGF.beta.. Together, these studies suggest that structural motifs common to TSP1 and **TSP2** inhibit endothelial **cell proliferation**. Furthermore, TSPs inhibit **cell proliferation** stimulated by two growth factor receptors that act through distinct signaling pathways.

L4 ANSWER 14 OF 16 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1995:971374 HCAPLUS
DOCUMENT NUMBER: 124:26270
TITLE: Expression of thrombospondins by endothelial cells: Injury is correlated with TSP-1
AUTHOR(S): Reed, May J.; Iruela-Arispe, Luisa; O'Brien, Edward R.; Truong, Thao; LaBell, Terry; Bornstein, Paul; Sage, E. Helene
CORPORATE SOURCE: Department Medicine, University Washington, Seattle, WA, 98195, USA
SOURCE: Am. J. Pathol. (1995), 147(4), 1068-80
CODEN: AJPAA4; ISSN: 0002-9440
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The thrombospondins (TSP-1, -2, and -3) comprise a family of proteins that are homologous at the carboxy terminus but have unique sequences at the amino terminus that might be correlated with the regulation of cell behavior. To investigate the expression of TSP-1, -2, and -3 in endothelial cells, we examd. developing murine blood vessels and human atherosclerotic plaques by in situ hybridization. The expression of TSP-1 was also characterized in cultured bovine aortic endothelial cells. Expression of **TSP-2** was seen in the dorsal aorta as early as embryonic day 10; TSP-1 was not detected in endothelial cells until later stages, and TSP-3 was not apparent in the vasculature. In atherosclerotic specimens, TSP-1 mRNA was detected in many intraplaque microvessels and in the endothelium lining the atheromatous plaque; **TSP-2** was absent from these regions. Cultured bovine aortic endothelial cells did not transcribe **TSP-2** mRNA at detectable levels. There were high steady-state levels of TSP-1 mRNA in subconfluent bovine aortic endothelial cells before confluence and at the wound edge after injury of the cell monolayer, with maximal expression of TSP-1 in cultures at a time during which approx. 35% of the cells were in S phase. As the majority of these cells subsequently undergo mitosis, these data are consistent with TSP-1 as an inhibitor of endothelial **cell proliferation** that functions in G1. These results support the conclusion that, despite sequence homol., the TSPs have distinct functions in vascular biol.

L4 ANSWER 15 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:576439 HCAPLUS
DOCUMENT NUMBER: 121:176439
TITLE: Tissue factor controls the balance of angiogenic and antiangiogenic properties of tumor cells in mice
AUTHOR(S): Zhang, Youming; Deng, Youhua; Luther, Thomas; Mueller, Martin; Ziegler, Reinhard; Waldherr, Ruediger; Stern, David Mark; Nawroth, Peter Paul
CORPORATE SOURCE: Dep. Medicine and Pathology, Univ. Heidelberg, Heidelberg, D-69115, Germany
SOURCE: J. Clin. Invest. (1994), 94(3), 1320-7
CODEN: JCINAO; ISSN: 0021-9738
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Meth-A sarcoma cells were stable transfected to overexpress (sense construct) or underexpress (antisense construct) tissue factor. In vitro, there was no difference in plating efficiency or growth between these cell

lines. In vivo, tumor cells transfected to overexpress tissue factor grew more rapidly, and established larger and more vascularized tumors than control transfectants. Antisense transfectants grew the slowest and were the least vascularized. Anticoagulation of mice with warfarin did not alter the difference between these tumor lines. Tumor cells overexpressing tissue factor released more (compared with control transfectants) mitogenic activity for endothelial cells in parallel with enhanced transcription of vascular permeability factor/vascular endothelial cell growth factor (VEGF/VPF), and diminished transcription of thrombospondin (**TSP2**), a mol. with anti-angiogenic properties. Antisense tissue factor transfectants, while releasing the lowest amt. of mitogenic activity, had increased thrombospondin and decreased VEGF/VPF transcription compared with control transfectants or wild-type cells. Expts. with these sense, antisense, truncated sense, or vector tumor lines gave comparable results in complete medium, serum free medium or in the presence of hirudin, indicating that the activation of the coagulation mechanism was not likely to be responsible for changes in tumor cell properties. These results suggest that tissue factor regulates angiogenic properties of tumor cells by altering the prodn. of growth regulatory mols. of endothelium by a mechanism distinct from tissue factor activation of the coagulation mechanism.

L4 ANSWER 16 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:163497 HCAPLUS
DOCUMENT NUMBER: 118:163497
TITLE: Characterization of mouse **thrombospondin 2** sequence and expression during cell growth and development
AUTHOR(S): Laherty, Carol D.; O'Rourke, Karen; Wolf, Frederick W.; Katz, Ronald; Seldin, Michael F.; Dixit, Vishva M.
CORPORATE SOURCE: Med. Sch., Univ. Michigan, Ann Arbor, MI, 48109, USA
SOURCE: J. Biol. Chem. (1992), 267(5), 3274-81
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Thrombospondin (TSP) is an extracellular matrix glycoprotein whose expression has been assocd. with a variety of cellular processes including growth and embryogenesis. The recent discovery of the existence of a second mouse TSP gene necessitates careful examn. of the discrete biochem. and functional properties assocd. with each mol. In this report, the primary structures of human TSP, mouse TSP1 (mTSP1), mouse **TSP2** (mTSP2), and chicken TSP are compared; and the expression of mTSP1 and mTSP2 during embryogenesis and growth factor-mediated **cell proliferation** is examd. The cloning and sequencing of the entire coding regions of mTSP1 and mTSP2 revealed considerable conservation of residues crit. for TSP structure and function; these data suggest that **TSP2** is capable of trimer formation and many of the same cell-surface and ligand interactions that mediate TSP function. Comparison of the various TSP sequences also allowed the assignment based on sequence homol. of previously reported human TSP as TSP1 and chicken TSP as **TSP2**. The mTSP2, like mTSP1, was shown to be a primary response gene when quiescent Swiss 3T3 cells were stimulated with serum, platelet-derived growth factor BB, basic fibroblast growth factor, or interleukin-1.beta.. Interestingly, TSP1 and **TSP2** exhibited

markedly different tissue- and stage-specific patterns of mRNA expression during mouse embryogenesis, implying that the two TSP mols. possess discrete functional properties important for development. Addnl., the TSP genes (Thbs1 and Thbs2) were mapped to single loci on mouse chromosomes 2 and 17, resp.